REMARKS

Claims 48-100 and 102-182 are pending in this application. No claim amendments, additions or cancellations have been effected by this Supplemental Response.

In their August 17, 1998 Supplemental Amendment, Applicants had amended independent claims 48, 77, 80, 100 and 102 by including as a material element therein a *quantifiable* soluble signal generated or generatable from a chemical label or labels which comprise a signaling moiety or moieties. In their earlier July 21, 1998 Amendment, Applicants had also submitted the Declaration of Dr. Dean L. Engelhardt in Support of Possession of Claimed Subject Matter and Novelty of Invention. In order to address further the anticipation issue with respect to the four *in situ* documents cited against the present invention, Applicants are submitting a Supplemental Declaration of Dr. Dean L. Engelhardt in Support of the Novelty of Invention and Claimed Subject Matter. This Supplemental Declaration is attached as Exhibit A and it takes into account the amendments effected by Applicants' August 17, 1998 Supplemental Amendment.

After reiterating his qualifications and professional experience from his previous Declaration, Dr. Engelhardt relays in Paragraph 3 his understanding of the pending claims in this application, including the amendments from Applicants' August 17, 1998 Supplemental Amendment to their July 21, 1998 Amendment Under §1.115. In Paragraph 4 of his Supplemental Declaration, Dr. Engelhardt reiterates the anticipation rejections from both the January 21, 1998 and October 2, 1995 Office Actions. As set forth in Paragraph 5, Dr. Engelhardt indicates that he is making this Declaration in support of the novelty of the invention defined by the pending claims, particularly reflected by the August 17, 1998 amendments. In the following paragraph (6), Dr. Engelhardt declares it to be his opinion and conclusion that none of the *in situ* documents cited against the pending claims disclose the instantly claimed element of a quantifiable soluble signal generated or generatable from a chemically labeled oligonucleotide or polynucleotide.

In Paragraph 7 (subparagraphs 7A through 7E), Dr. Engelhardt provides background for *in situ* hybridization, citing three early scientific papers in

subparagrph A, several nucleic acid textbooks in subparagraph B, *in situ* hybridization textbooks in subparagraph C, scientific and technical definitions in subparagraph D, and the work of the renown Dr. David C. Ward of Yale University in subparagraph E. Continuing in Paragraph 8, Dr. Engelhardt notes that each of the cited documents (Stuart et al., Langer-Safer et al., Manuelidis et al. and Ward et al.):

> . . . is limited to *in situ* hybridization which can only be practiced in the context of clear boundaries and well-defined morphology against which a localized signal - and not a soluble signal let alone a quantifiable soluble signal - must be produced and interpreted. The quantifiable soluble signal which is a material element in the pending claims of this application is in no way localized nor is morphology either required, maintained or viewed. Indeed, with the generation of a quantifiable soluble signal, a dispersed or scattered signal in solution is obtained without any regard to any limitation or requirement for morphologic integrity.

Dr. Engelhardt ends the paragraph, concluding that:

> with their preoccupation on morphologic integrity (landmarks, boundaries and the like) and a localized signal (and not a quantifiable soluble signal), the four prior art *in situ* hybridization documents actually teach away from the invention set forth in the present claims. As a material element in the present invention, the quantifiable soluble signal requires neither localization nor morphologic integrity of the prior art *in situ* hybridization disclosures.

In Paragraph 9, Dr. Engelhardt distinguishes the novelty of the present invention from Stuart et al. on the basis of two material elements defined by the pending claims. As explained in subparagraph A, Stuart et al. is wholly and only concerned with *in situ* hybridization and thus, requires morphologic integrity and a localized signal - not a quantifiable signal as defined by the present claims of this application. Dr. Engelhardt also explains in subparagraph B that unlike the instant invention which calls for and requires a chemical label or labels on one of the nucleic acid strands, Stuart et al. do not disclose or even suggest any such modification for any nucleic acid, particularly because Stuart's assay is strictly and only an immunoassay. As noted by Dr. Engelhardt, Stuart et al. employ such labeled monoclonal antibodies (or antibodies) for the sole purpose of detecting *immunologically* the hybrid DNA-RNA complex (quoting column 4, lines 24-55 in Stuart's patent). In contrast to the presently claimed invention, the DNA-RNA

hybrid complex in Stuart's disclosure is in no way chemically labeled.

Dr. Engelhardt addresses Langer-Safer et al. and Manuelidis et al. in Paragraph 10 of his Supplemental Declaration. He notes that "both articles teach away from the instant invention because *in situ* hybridization requires morphologic integrity and localized signal production - and not a quantifiable soluble signal as embodied materially in the present claim elements." According to Dr. Engelhardt, this is a significant distinction between *in situ* hybridization, immunoprecipitates and insoluble signal on the one hand, and the instantly recited quantifiable soluble signal on the other. Dr. Engelhardt explains further:

> When performing *in situ* hybridization, the technician or researcher is looking under the microscope and observing form or morphology as well as signalling events within the context of any such form or morphology. Such a person only observes and amasses information within the context of clearly defined boundaries and visible shapes. The cells or the contents of cells under examination must have such boundaries and shapes in order to carry out detection in *in situ* hybridization. Separation and analytical techniques are largely based on precipitates and defined boundaries. With soluble signals, however, the approach is entirely antithetical to the purposes of and the information being sought through light microscopic examination. With a quantifiable soluble signals, however, there are no clearly defined boundaries, shapes and morphology with which the technician or researcher must contend. In fact, the technician or research is concerned with the total amount of target nuclec acid analyte in the sample or specimen - and not with its location or distribution in the cells or tissues. Thus, *in situ* hybridization as disclosed in the Langer-Safer and Manuelidis et al. documents teaches away from the instant invention. By directing and focusing attention to morphology and localized signaling, both of which are required in *in situ* hybridization, Langer-Safter et al. and Manuelidis et al. actually discourage any resort to a quantifiable soluble signal. Indeed, for the skilled artisan to go from precipitates and insoluble signals to a quantifiable soluble signal, all prior conceptions and experiences relating to detection (localized signals) and observation (morphologic integrity) would have to be abandoned altogether.

With respect to Ward et al., Dr. Engelhardt points out in Paragraph 11 that this document is also wholly concerned with immunoprecipates, precipitated signals, insoluble colored precipitates and the like (quoting column 21, first paragraph, lines 4-24 in Ward et al.). Dr. Engelhardt points out further that Ward and his group are working with the enzyme peroxidase in what are clearly insoluble precipitates for light microscope visualization (quoting column 24, lines 33-62, in

Ward et al.). Dr. Engelhardt concludes the paragraph, noting that "the focus of Ward et al. is on insoluble colored precipitates and direct light microscopic visualization which elements are diametrically opposed to and actually teach away from the present invention and the notion of a quantifiable soluble signal."

In view of Dr. Engelhardt's Supplemental Declaration and the attached exhibits (1-12), Applicants respectfully request reconsideration and withdrawal of the three anticipation rejections based upon the four cited documents, Stuart et al., Langer-Safer et al., Manuelidis et al. and Ward et al. Upon withdrawal of the these anticipation rejections, it is believed that the pending claims will be in otherwise allowable condition for issuance. An early indication as to the allowability of the present claims is in order and earnestly sought.

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SUMMARY AND CONCLUSIONS

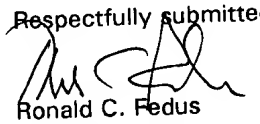
No claims have been added or canceled by this Supplemental Response. Thus, claims 48-100 and 102-182 are presented once again for substantive examination on the merits.

No fee is believed due in connection with this Supplemental Response, a three month extension fee having been previously authorized in connection with Applicants' July 21, 1998 Amendment Under 37 C.F.R. §1.115 and referenced in their August 17, 1998 Supplemental Amendment. In the event, however, that any other fee or fees are due in connection with this Supplemental Response or with any of Applicants' previous responses, the Patent and Trademark Office is hereby authorized to charge the amount of any such fee(s) to Deposit Account No. 05-1135, or to credit any overpayment thereto.

If it would be helpful to expediting the prosecution of this application, the undersigned may be contacted by telephone at 212-583-0100 during the daytime business hours.

Early and favorable action on this application is respectfully sought.

Respectfully submitted



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